REMARKS

Claims 6-16, 18-27, 29-37 and 44 are pending in the above-identified application.

Applicant respectfully submits that, in contrast to item 4 in the Office Action Summaries of the Office Actions mailed July 17, 2001 and January 10, 2002, claim 18 is pending in the above-identified application. In this regard, claim 18 was correctly identified as pending in the Office Action mailed November 21, 2000, and claim 18 has not been cancelled by the Applicant.

By the present communication claims 9, 10 and 15 have been cancelled without prejudice to pursuing the subject matter of these claims in one or more applications claiming the benefit of priority to the above-identified application. Furthermore, claims 6-8, 11, 13, 14, 25-27, 29-32, 34-37 and 44 have been amended. Following entry of the present amendment, claims 6-8, 11-14, 16, 18-27, 29-37 and 44 will be pending.

Claims 6-8, 11, 13, 14, 25-27, 29-32, 34-37 and 44 have been amended to recite BAG-1, support for which can be found in the specification including, for example, on page 9, line 1, through page 11, line 14; page 12, lines 5-8 and page 32, line 1, through page 36, line 6. Claims 16, 25, 27, 34 and 44 have been

amended to recite stage I or stage II cancer, support for which can be found in the specification including, for example, on page 25, line 7, through page 26, line 2 and page 32, line 1, through page 36, line 6. Accordingly, the amendments do not introduce new matter. Therefore, entry of the amendments is respectfully requested. A marked-up copy of the claims showing the amendments is attached hereto as Appendix A.

Applicant respectfully traverses the rejection of claims 6-16, 19-27, 29-37 and 44, under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Applicant maintains, for the reasons of record, that the specification is sufficiently enabling for claims 6-16, 18-27, 29-37 and 44. Nevertheless, in order to further prosecution of this application, claims 9, 10 and 15 have been cancelled and claims 6-8, 11, 13, 14, 25-27, 29-32, 34-37 and 44 have been amended.

Following entry of the amendments, claims 6-16 and 18-24 will be directed to a method for prognosis of disease-free or overall survival of an individual having a cancer tumor by determining the level of BAG-1 expression in a sample of the tumor or a body fluid during stage I or stage II of the cancer, wherein a high level of BAG-1 expression correlates positively with disease-free or overall survival, wherein the cancer is breast cancer. Applicant respectfully submits that following entry of the amendments, claims 6-16 and 18-24 will be in accordance with the subject matter which the Office Action

asserts to be enabled, in stating on page 3, lines 1-7, that the specification is enabling for detecting increased BAG-1 as an indicator of increased overall survival or distant metastasis free survival in Stage I or Stage II breast cancer patients.

Applicant respectfully submits that the specification is sufficiently enabling for the methods recited in claims 25-27, 29-37 and 44, as amended. The specification provides working examples demonstrating that BAG-1 immunostaining was upregulated in stage I and stage II breast cancer cells compared to normal breast epithelium cells (see page 34, lines 17-28) and that increased BAG-1 expression level was correlated with increased overall survival or disease-free survival in patients with stage I or stage II breast cancer (see page 35, lines 5-23). The specification further teaches on page 35, line 32, through page 36 that

> patients whose tumors contain high levels of cytosolic BAG-1 protein are more likely to enjoy long-term survival and freedom from tumor recurrence or spread and distant metastases, compared to those with tumors containing low levels of cytosolic BAG-1.

In view of the teaching and guidance provided in the specification, those skilled in the art would have been able to use claims 25 and 26, which are directed to a method of predicting the risk of tumor recurrence or spread in an individual; claim 44, which is directed to a method of

determining a prognosis in a patient suffering from cancer, wherein patients are classified according to a correlation between BAG-1 expression and likelihood of tumor recurrence or spread; and claims 27 and 29-33, which are directed to a method of determining the risk of tumor metastasis.

Upon entry of the amendments, claim 34 will be directed to a method for determining the proper course of treatment for a patient suffering from cancer by determining the level of BAG-1 expression in a cancerous tissue sample or body fluid from the patient during stage I or stage II of the cancer; identifying a first group of patients having low levels of BAG-1 expression, which first group of patients may require treatment proper for patients having a lesser chance of survival or decreased time to tumor recurrence or spread; and identifying a second group of patients having high levels of BAG-1 expression, which second group of patients may require treatment proper for patients having a greater chance of survival and being less likely to suffer tumor recurrence or spread. As taught on page 28, lines 10-14 of the specification, appropriate treatments for patients having greater or lesser chances of survival will be determined with proper consideration of other factors, by one of ordinary skill in the art according to the available therapeutic methods. The specification further teaches a variety of therapeutic methods that can be used such as surgery, chemotherapy, radiation, and the like (see, for example page 28, lines 14-22). In view of the guidance provided in the specification and that which was known in the art regarding available therapeutic

treatments for breast cancer, those skilled in the art would have been able to use the methods of amended claims 34-37 to determine the proper course of treatment for a patient suffering from cancer.

Applicant respectfully submits that the references by Tang et al. (J. Clin. Oncol. 17:1710-1719(1999)), Zapata et al. (Breast Canc. Res. Treat. 47:129-140(1998)), Yawata et al. (Oncogene 16:2681-2686(1998)) and Takaoka et al. (Oncogene 14:2971-2977 (1997)) are non-analogous to the amended claims for the following reasons. As set forth previously on the record, the disclosure in Tang et al. that BAG-1 overexpression may be associated with a shorter disease-free and overall survival is based on an analysis of BAG-1 overexpression in all stages of breast cancer. However, Tang et al. does not describe a statistically significant correlation between BAG-1 expression and disease-free and overall survival for stage I or stage II breast cancer. Because a statistically relevant correlation between BAG-1 expression and disease-free or overall survival at a particular stage of breast cancer cannot be reliably determined from the results presented by Tang et al., the reference does not support unpredictability of the claimed methods, which are directed to correlations of BAG-1 expression with stage I or stage II breast cancer.

The reference by Zapata et al. is non-analogous to the claimed methods because Zapata et al. merely describes that the

intensity of BAG-1 immunostaining was often higher in invasive breast cancers compared to normal epithelium. Zapata et al. does not describe any correlation of BAG-1 expression to the clinical outcomes recited in the claims including, for example, disease free or overall survival, risk of tumor recurrence or spread, risk of tumor metastasis or determination of a proper course of treatment. Absent description of any correlation of BAG-1 expression to the clinical outcomes recited in the claims, Zapata et al. is non-analogous to the claims as amended.

The references by Yawata et al. and Takaoka et al. are related to human gastric carcinoma and murine melanoma, respectively. Nowhere does Yawata et al. or Takaoka et al. describe any correlation between BAG-1 expression and breast cancer, much less stage I or stage II breast cancer. Absent description in Yawata et al. or Takaoka et al. of a correlation between BAG-1 expression and stage I or stage II breast cancer, as claimed, these references are non-analogous to the claimed methods.

Because the references by Tang et al., Zapata et al., Yawata et al. and Takaoka et al. are non-analogous to the claims as amended, the assertions in the Office Action that the art pertaining to the claimed methods is unpredictable are unfounded.

Applicant respectfully submits that for the reasons set forth above, the specification is sufficiently enabling for the

full scope of the amended claims. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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APPENDIX A

A marked up version of the claims showing amendments is provided below. For the convenience of the Examiner, the full set of claims following entry of the amendments is provided and the claims are grouped together according to subject matter rather than in numerical order.

16. (Twice amended) A method for prognosis of disease-free or overall survival of an individual having a cancer tumor, comprising determining the level of BAG-1 [BAG gene] expression in a sample of said tumor or a body fluid during stage I or stage II of said cancer, wherein a high level of BAG-1 expression correlates positively with disease-free or overall survival, wherein said cancer is breast cancer.

18. (Twice amended) The method of claim 16, wherein said level of BAG-1 [BAG] expression is determined by measuring the level of mRNA encoding BAG-1 [encoded by said BAG gene].

19. (Amended) The method of claim 16, wherein said level of BAG-1 [BAG] expression is determined by measuring BAG-1 [BAG] protein levels.

20. (Amended) The method of claim 16, wherein said level of BAG-1 [BAG] expression is determined by measuring the level of BAG-1 [BAG] protein that is detectable in samples selected from the group consisting of breast tumor tissue, blood, serum, and plasma.

21. (Amended) The method of claim 16, further comprising determining if said level of BAG-1 [BAG] expression represents an overproduction that is above a reference level of BAG-1 [BAG] expression.

22. (Amended) The method of claim 21, wherein said reference level of BAG-1 [BAG] expression is determined by a histogram analysis.

23. (Amended) The method of claim 21, wherein said reference level of BAG-1 [BAG] expression is determined relative to a level of BAG-1 [BAG] expression produced by *in vitro* cultured cells which produce BAG-1 [BAG].

24. (Amended) The method of claim 21, wherein said reference level of BAG-1 [BAG] expression is determined relative to a level of BAG-1 [BAG] expression in non-cancerous cells.

6. (Twice amended) The method of claim 16, wherein said [expression] level of BAG-1 expression [the BAG gene] is

determined by measuring the amount of the BAG-1 [BAG] mRNA transcript or BAG-1 [BAG] protein.

7. (Amended) The method of claim 6, wherein said measuring the amount of BAG-1 [BAG] protein is with an agent that binds BAG-1 [BAG] protein.

8. (Amended) The method of claim 7, wherein said agent is an antibody specific for the BAG-1 [BAG] protein.

11. (Amended) The method of claim 6, wherein said [expression] level of BAG-1 expression [the BAG gene] is determined by measuring the amount of BAG-1 [BAG] protein product using an immunoassay.

12. The method of claim 11, wherein said immunoassay is an immuno-polymerase chain reaction (immuno-PCR) assay.

13. (Twice amended) The method of claim 16, wherein said [expression] level of BAG-1 expression [the BAG gene] is determined prior to lymph node involvement of said cancer.

14. (Twice amended) The method of claim 16, wherein said [expression] level of BAG-1 expression [the BAG gene] is determined after lymph node involvement of said cancer.

25. (Twice amended) A method for predicting the risk of tumor recurrence or spread in an individual having a cancer tumor, comprising determining whether BAG-1 [BAG] protein is produced in a sample of said tumor or body fluid from said individual, such a production correlating negatively with a likelihood of tumor recurrence or spread, wherein said cancer is stage I or stage II breast cancer.

26. (Amended) The method of claim 25, further comprising:

(a) determining an overproduction level for BAG-1 [BAG] protein, said level being in excess of a minimum amount statistically determined to be indicative of decreased likelihood of tumor recurrence or spread;

(b) determining the level of BAG-1 [BAG] expression in said tumor sample; and

(c) predicting said risk of tumor recurrence or spread wherein an overproduction level of BAG-1 [BAG] protein in the tumor sample is negatively associated with the likelihood of tumor recurrence or spread.

27. (Twice amended) A method for screening a cancer patient to determine the risk of tumor metastasis, said method comprising:

(a) determining the level of amplification or expression of BAG-1 [the BAG gene] in a cancerous tissue sample or a body fluid sample from said patient during stage I or stage II of said cancer; and

(b) classifying a patient having high levels of amplification or expression of BAG-1 [the BAG gene], relative to a reference level, as being less likely to suffer tumor metastasis or having a increased chance of survival,

wherein said cancer is breast cancer.

29. (Amended) The method of claim 27, wherein BAG-1 [BAG] amplification is measured with a probe specific for BAG-1 [the BAG gene].

30. (Amended) The method of claim 27, wherein gene expression is determined by measuring the amount of BAG-1 [BAG] mRNA transcription.

31. (Amended) The method of claim 27, wherein gene expression is determined by measuring the amount of BAG-1 [BAG] protein.

32. (Amended) The method of claim 31, wherein the amount of BAG-1 [BAG] protein is measured using an immunoassay.

33. The method of claim 32, wherein said immunoassay is an immuno-polymerase chain reaction assay.

34. (Twice amended) A method for determining the proper course of treatment for a patient suffering from cancer, said method comprising:

(a) determining the level of BAG-1 [BAG gene] expression in a cancerous tissue sample or body fluid from said patient during stage I or stage II of said cancer;

(b) identifying a first group of patients having low levels of BAG-1 [BAG gene] expression, which first group of patients may require treatment proper for patients having a lesser chance of survival or decreased time to tumor recurrence or spread; and

(c) identifying a second group of patients having high levels of BAG-1 [BAG gene] expression, which second group of patients may require treatment proper for patients having a greater chance of survival and being less likely to suffer tumor recurrence or spread,

wherein said cancer is breast cancer.

35. (Amended) The method of claim 34, wherein said level of BAG-1 [BAG gene] expression is determined by measuring the amount of BAG-1 [BAG] mRNA transcript or BAG protein.

36. (Amended) The method of claim 34, wherein said level of BAG-1 [BAG gene] expression is determined prior to lymph node involvement.

37. (Amended) The method of claim 34, wherein said level of BAG-1 expression [of the BAG gene] is determined after lymph node involvement of said cancer.

44. (Thrice amended) A method for determining a prognosis in a patient suffering from cancer, said method comprising:

(a) determining the level of expression of BAG-1 [BAG] in cancerous tissues of a patient during stage I or stage II of said cancer; and

(b) classifying said patient as belonging either to a first group of patients having high levels of expression of BAG-1 [BAG], or a second group of patients having low levels of expression of BAG-1 [BAG],

wherein said first group has a lower likelihood of tumor recurrence or spread than said second group, and wherein said cancer is breast cancer.